REMARKS/ARGUMENTS

In response to the Office Action of January 5, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer markers of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation

error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers, clearly indicate that Figures 2, 3 and 5 show the mass spectrum profiles of the disclosed biopolymer markers, and to remove the term "specimen" from the description of Figures 1 and 4.

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (line 10), page 42 (lines 1 and 16) and and page 43 (lines 7 and 20)were underlined in the original disclosure and do not indicate text amended herein (with the exception of the term "SEPHAROSE").

The paragraph at page 46 was amended in order to complete the sentence.; i.e. the peptides were found through practicing the disclosed procedures.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 16 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation

for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer markers (SEQ ID NOS:1-3). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer markers (SEQ ID NOS:1-3) and Type II diabetes. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer markers are determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 8-18 and Figures 1-5.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 14 to page 48, line 23. Claim

44 was also amended to correct a grammatical error(an replaced and).

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

Applicants thank the Examiner for the withdrawal of the restriction between SEQ ID NOS:1-3 of record in the Office Action mailed on October 6, 2004.

While the restriction of SEQ ID NOS:1-3 has been withdrawn, it appears that the rejections are drawn only to SEQ ID NO:1. Therefore, Applicants have amended the claims to encompass SEQ ID NOS:1-3 but have addressed the rejections as drawn to SEQ ID NO:1 only.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NOS:1-3 a search of these claims would encompass these specific peptides. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants

respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptides of SEQ ID NOS:1-3 are found to be novel, methods and kits limited to their use should also be found novel.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statements filed on March 12, 2002 and September 29, 2003 have been considered as to the merits prior to the first action.

The references cited within the specification but not included

in the above-mentioned Information Disclosure Statements provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Oath/Declaration

A new oath or declaration has been required by the Examiner because while the original oath filed on February 13, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature is omitted.

A new Declaration which is properly executed is filed herewith.

Objections to the Specification

The Examiner notes that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors.

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE at page 41, lines 4 and 5 and TRITON at page 42, line 12) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be

respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 40-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Rejection under 35 USC 112, second paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that claim 1 is vague and indefinite because the biopolymer is "diagnostic" for Type II diabetes. "Diagnostic" reads on not only the detection of the disease but

also the analysis of the cause or nature of the disease. It is not clear how the biopolymer marker will analyze the cause or nature of Type II diabetes. Applicants' intended meaning of "diagnostic" is not defined by the claims or the specification. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner suggests that the claim merely recite "detection of" Type II diabetes in order to obviate this rejection.

Applicants respectfully disagree with the Examiner's assertions.

The term "diagnostic" refers to the identification of a property or characteristic, usually regarding the health of an individual, such as, identifying a disease linked with the property or characteristic. It is clear from the multiple disclosures in the instant specification that the term "diagnostic" or "diagnose" refers to the identification of a disease; see, for example, page 5, lines 12-20; page 31, lines 19-22; page 32, lines 7-10; page 36, lines 9-12; page 48, lines 9-11; page 52, lines 10-13 and page 53, lines 1-8. According to the web site dictionary. com; the term "diagnostic" relates to or refers to use in diagnosis; use in serving to identify a particular disease or to a symptom or a distinguishing feature; and/or use in serving as supporting

evidence in a diagnosis (see attached definition as accessed from the internet; reference 1).

Neither the art nor the specification suggests that "diagnostic" refers to anything other than identification of a disease. Thus, Applicants respectfully submit that the Examiner has no basis for asserting that the term "diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease.

However, in the interest of compact, efficient prosecution, Applicants have amended the claim to remove the term "diagnostic".

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 101

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 101 because the claimed invention allegedly is not supported by a either a specific, substantial, credible or asserted utility or a well-established utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility that was evident at the

time of filing.

The Examiner asserts that applicants have disclosed in the specification that SEQ ID NO:1 is measurable in normal patients but non detectable in Type II diabetes. See page 46, lines 8-18.

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Page 46 of the instant specification indicates that practice of the disclosed procedures identifies the peptide of SEQ ID NO:1 as predictive of Type II diabetes. Contrary to the Examiner's assertion no disclosures and/or assumptions about the presence and/or regulation of the peptide (SEQ ID NO:1) are found at page 46 of the instant specification.

Additionally, the Examiner asserts that the disclosure appears to require not only SEQ ID NO:1 but a combination of SEQ ID NOS:1-3 for the identification of Type II diabetes.

Applicants respectfully assert that this statement made by the Examiner is also incorrect.

No where does the specification indicate that a combination of markers (SEQ ID NOS:1-3) is an absolute requirement for the identification of Type II diabetes through use of the disclosed methods.

The Examiner asserts that applicant sets forth Figure 1 as evidence of SEQ ID NO:1 as a marker for Type II diabetes. However,

Figure 1 appears to show SEQ ID NO:1 in normal patients as well as in Type II diabetes patients. According to the Examiner, no clear difference in up and down regulation of the marker can be determined.

Applicants respectfully disagree with the Examiner's interpretation of the data.

Lane 2 (as read from the left) of the gel shown in Figure 1 contains a sample obtained from a patient determined to be normal with regard to Type II diabetes. Complement fragments were identified in Band #3-2 excised from lane 2.

Lane 10 (as read from the left) of the gel shown in Figure 4 also contains a sample obtained from a patient determined to be normal with regard to Type II diabetes. Complement fragments were identified in Band #2 excised from lane 10.

Lane 3 (as read from the left) of the gel shown in Figure 4 also contains a sample obtained from a patient having Type II diabetes. Complement fragments were identified in Band #4 excised from lane 3.

However, it is important to note, that the complement fragments found in Type II diabetes were of a lighter weight as compared to the fragments found in patients determined to be normal (see especially Figure 4).

Thus, contrary to the Examiner's assertion, a clear difference

in up and down regulation of the marker between both states (Type II diabetes versus normal) can be determined.

The Examiner further asserts that SEQ ID NO:4 does not appear to be a marker for Type II diabetes (clearly distinguishing the disease from control or normal patients).

Applicants respectfully disagree with the Examiner's line of reasoning and assert that SEQ ID NO:1 is useful for diagnosis and treatment of Type II diabetes since it was found to evidence a link to Type II diabetes (an "asserted" utility). This asserted utility is supported by data derived from the working examples (gels shown in Figures 1 and 4), which shows that the claimed peptide is differentially expressed between Type II diabetes and normal.

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed peptide (SEQ ID NO:1).

Additionally, it has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP

2107.02 III B).

Thus, Applicants respectfully assert that it is improper for the Examiner to state that SEQ ID NO:1 does not appear to be a marker for Type II diabetes.

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, lines 8-18; and Figures 1 and 4).

The claimed peptide (SEQ ID NO:1) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, Type II diabetes, thus the invention has a specific utility.

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The incidence of Type II diabetes is rising in westernized countries. Thus, advances in diagnosis and treatment of Type II diabetes would greatly benefit the population of westernized countries. The claimed peptide (SEQ ID NO:1) represents an advance in diabetes research; a "real-world" use benefitting the public (i.e. the population of westernized countries), which satisfies the precedent set in *Nelson*. Thus, the claimed peptide (SEQ ID NO:1)

additionally has a substantial utility based upon a "real-world" use.

In the search for specific biomarkers proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. For example, when a peptide is identified in a body fluid sample from an Alzheimer's patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 2) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker. Thus, when one of skill in the art observes the claimed peptide differentially expressed between Type II diabetes patients and normal, control patients; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for Type II diabetes and would immediately appreciate why applicants regard the claimed peptide (SEQ ID NO:1) as useful, indicating that the utility of the claimed peptide (SEQ ID NO:1)

is well-established.

Activation of the complement system has long been suspected to play a role in the development of Type II diabetes and heart disease (see attached abstract of Figueredo et al. Diabetes Care 16(2)445-449 1993; reference 3). Additionally, plasma levels of complement factor 3 are known to be elevated in Type II diabetes and subjected to proteolysis, thus complement C3 becomes fragmented in Type II diabetes (see attached abstract of Krantz et al. Experimental Clinical Endocrinology 92(3):287-296 1988; reference 4).

At page 46 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:1) is identified as a fragment of complement C3f precursor protein. Furthermore, Figures 1 and 4 demonstrate that complement is fragmented in Type II diabetes. The instant inventors hypothesized that the claimed peptide may signify active proteolysis and thus may represent a potential marker for Type II diabetes and its associated cardiovascular complications. One of skill in the art considering that increased plasma levels of fragmented complement C3 have been documented in diabetic patients would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1 and Type II diabetes and thus would also find the suggestion of SEQ ID NO:1 as a marker for Type II

diabetes entirely possible.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, first paragraph. Specifically the Examiner asserts that since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

It has been established by prior arguments in the instant Response that the claimed invention has both a specific and a well established utility. Therefore, Applicants respectfully request that the Examiner now withdraw the rejection under 35 USC 112, first paragraph which was based upon the rejection under 35 USC 101.

Claim 1, as presented on December 10, 2004, stands further rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner makes the following assertions:

Claim 1 is directed to a biopolymer consisting of SEQ ID NO:1 diagnostic for Type II diabetes. The Examiner contends that the specification does not support this assertion. The specification (in particular page 46) and figure 1 do not definitively correlate the absence of the claimed marker consisting of SEQ ID NO:1 in Type II diabetes. The specification recites that the biopolymer consisting of SEQ ID NO:1 was found in the serum of normal patients but not in patients suffering from Type II diabetes on page 46, but the specification does not contain any data supporting this contention and the figures exemplify SEQ ID NO:1 in both normal and Type II diabetes patients (see figure 1 Band 3-2). Therefore, it is unclear how SEQ ID NO:1 was identified as "notable" or how it was deemed "evidentiary" of a disease state (Type II diabetes). There is nothing in the disclosure that would enable one to choose SEQ ID NO:1 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

Although Applicants believe that the instant specification,

as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:1 is diagnostic for Type II diabetes, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:1 is linked to Type II diabetes.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 5). The instant specification fully supports a connection and/or an association of the claimed peptide with Type II diabetes. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be

conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:1) is linked and/or associated with Type II diabetes.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:1, a peptide which the instant specification identifies as related to Type II diabetes. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for Type II diabetes, nor does it recite that the claimed isolated peptide is related to Type II diabetes, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

Figure 4 demonstrates that the complement protein is fragmented in Type II diabetes (Band #4 compared to Band #2). Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to Type II diabetes.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained from the disclosed

method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 47, lines 3-5 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 6). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 11-15 of the instant specification as originally filed, and Figures 1 and 4). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the

method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 4 from which the claimed peptide was identified (SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-

disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 4 is a photograph of a gel showing the results of HiQ3 (scrub) column chromatography as carried out with a set of nine samples; 5 serum samples obtained from Type II diabetes patients (lanes 2-6, as read from the left) and 4 serum samples obtained from patients who were determined to be normal with regard to Type II diabetes (lanes 7-10, as read from the left). Lane 1 was reserved for the molecular weight standards. Lane 10 (as read from the left) of the gel shown in Figure 4 also contains a sample obtained from a patient determined to be normal with regard to Type II diabetes. Complement fragments were identified in Band #2 excised from lane 10.

Lane 3 (as read from the left) of the gel shown in Figure 4 also contains a sample obtained from a patient having Type II diabetes. Complement fragments were identified in Band #4 excised from lane 3.

However, it is important to note, that the complement fragments found in Type II diabetes were of a lighter weight as compared to the fragments found in patients determined to be normal.

The data presented in the figures, derived from the working examples, discloses that the claimed peptide (SEQ ID NO:1) is differentially expressed between Type II diabetes and a "normal" physiological state regarding diabetes, thus it can be reasonably predicted that such peptide is linked to Type II diabetes. Furthermore, the figures identify SEQ ID NO:1 and the specification discloses how such a sequence was identified as a notable sequence in relation to Type II diabetes.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and Type II diabetes.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that the specification does not enable

one of ordinary skill in the art to definitely assess the incidence of the disease in a single test sample. Furthermore, the Examiner asserts that there is no correlation between the procedure for screening samples from patients suspected of having a variety of different diseases, the presence/absence of SEQ ID NO:1; and the determination, prediction, assessment of Type II diabetes. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence. The disclosure is lacking any teaching for how the identified sequence will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequence could be utilized therein, enabling one of ordinary skill in the art to use the sequence in the diagnostic method.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any methods which definitively assess the incidence of Type II diabetes or any other disease state. Furthermore, the pending claims do not recite any disease state other than Type II diabetes, nor do the pending

claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that SEQ ID NO:1 is a unique molecular markers for Type II diabetes or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that SEQ ID NO:1 is linked to Type II diabetes, however, do not claim that SEQ ID NO:1 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:1, a fragment of complement C3f precursor,

is related to Type II diabetes, it does recognize that activation of the complement system has long been suspected to play a role in the development of Type II diabetes and heart disease (see attached abstract of Figueredo et al. Diabetes Care 16(2)445-449 1993; reference 3). Additionally, plasma levels of complement factor 3 are known to be elevated in Type II diabetes and subjected to proteolysis, thus complement C3 becomes fragmented in Type II diabetes (see attached abstract of Krantz et al. Experimental Clinical Endocrinology 92(3):287-296 1988; reference 4). When one of skill in the art observes differential expression of the claimed peptide between Type II diabetic patients and non-diabetic patients; one of skill in the art will connect this peptide with potential diagnostic and/or therapeutics for Type II diabetes.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide (SEQ ID NO:1) and Type II diabetes and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of Type II diabetes, the requirement of "how to use" under 35 USC 122, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and Type II diabetes to be reasonable.

At page 46 of the instant specification as originally filed, the claimed peptide (SEQ ID NO:1) is identified as a fragment of complement C3f precursor protein. Furthermore, Figures 1 and 4 demonstrate that complement is fragmented in Type II diabetes. The instant inventors hypothesized that the claimed peptide may signify active proteolysis and thus may represent a potential marker for Type II diabetes and its associated cardiovascular complications. One of skill in the art considering that increased plasma levels of fragmented complement C3 have been documented in diabetic patients would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1 and Type II diabetes and thus would also find the suggestion of SEQ ID NO:1 as a marker for Type II diabetes entirely possible.

The Examiner asserts that the disclosure has not addressed issues taught in the prior art as crucial to the discovery of a biopolymer marker.

The Examiner cites two articles; Tascilar *et al.* (Annals of Oncology 10, Supplement 4:S107-S110 1999) and Tockman *et al.* (Cancer Research 52:2711s-2718s 1992) which are allegedly relevant to the instant invention.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods

in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods of the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently". The Examiner appears to be commenting on the predictability of molecular-based assays.

Applicants respectfully disagree with the Examiner's reliance on the article by Tascilar et al.

Applicants assert that the claimed peptide (SEQ ID NO:1) is linked to Type II diabetes; a statement which is enabled by the description of methods as set forth in the specification and by data presented in Figures 1 and 4. Thus, applicants respectfully submit that the claimed method involves a simple observation of the levels of expression of SEQ ID NO:1 (as shown in Figure 4) and does not require any other evaluation of genetic changes in the organism in which the sequence is observed.

Furthermore, the study of Tascilar et al. is concerned with the evaluation of samples for genetic mutations (K-ras and p53 mutations) for early detection of pancreatic cancer (see attached abstract of Tascilar et al. Annals of Oncology 10, Supplement

4:S107-S110 1999; reference 7). It appears that Tascilar et al. suggest that protein markers may be useful for early detection of pancreatic cancer; however there does not seem to be any other reference to protein markers, thus the study of the instant inventors (drawn to protein markers and not to genetic markers) is not analogous to the study of Tascilar et al.

Accordingly, Applicants respectfully submit that the Tascilar *et al.* article is not relevant to the instant invention.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al* is deemed to teach that the essential

element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for Type II diabetes.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any

"criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and Type II diabetes.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

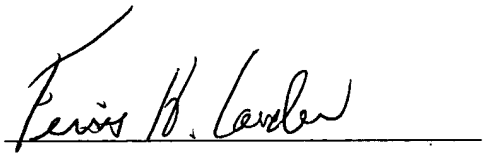
The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:1 between Type II diabetes patients and patients determined to be normal with regard to Type II diabetes evidences a link between the claimed peptide (SEQ ID NO:1) and Type II diabetes; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:1) and Type II diabetes and would further recognize how to use the claimed peptide (SEQ ID NO:1) as a marker for Type II diabetes. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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